A computational Model to Assess the Contribution of Growth Factors to Phenotype Stability in Chondrocytes

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INTRODUCTION

Background
- Developmental engineering: an in vivo-like in vitro process to engineer tissues[1]
- Understanding of combination and interplay of signals directing chondrocyte development is required

Growth plate regulation
- BMP, Wnt, FGF, Ihh/PTHrP, TGFβ and IGF-I are important paracrine signals
- Sox9 is the master regulator of chondrogenesis
- Runx2 controls chondrocyte hypertrophy

Modelling
- Multiple cross-talks turn linear signalling cascades into a complex network
- Models can assist in interpretation and evaluation of qualitative network behaviour

MATERIALS & METHODS

- A **literature-based network** comprising several influences on the balance between Sox9 and Runx2
  - Wnt
  - BMP
  - FGF
  - Ihh/PTHrP
  - IGF-I
  - TGF β
- 46 nodes and 161 interactions
- **ODE** simulation using **additive** functions
- The stable state is equated with a cell type, i.e. a **proliferative chondrocyte** in the case of a **Sox9-positive** state and a **hypertrophic chondrocyte** in the case of a **Runx2-positive** state

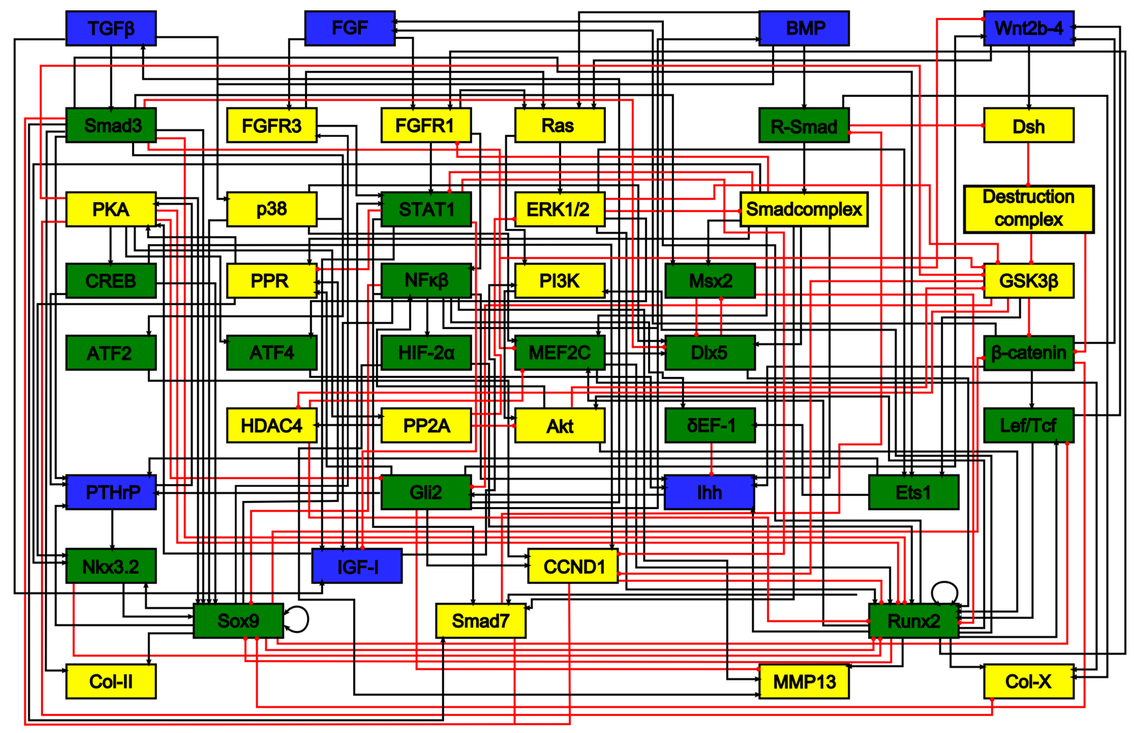

Figure 1: The chondrocyte gene network

PHENOTYPICAL STABILITY

- **Stability to perturbation** in a random node
- Shows **higher stability** of Runx2 state

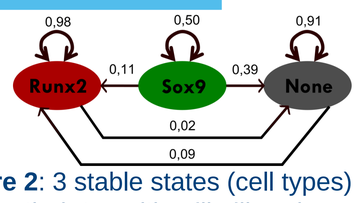

Figure 2: 3 stable states (cell types) and their transition likelihoods

STABILITY OF CARTILAGE

- What is the contribution of individual 'maintenance' factors?

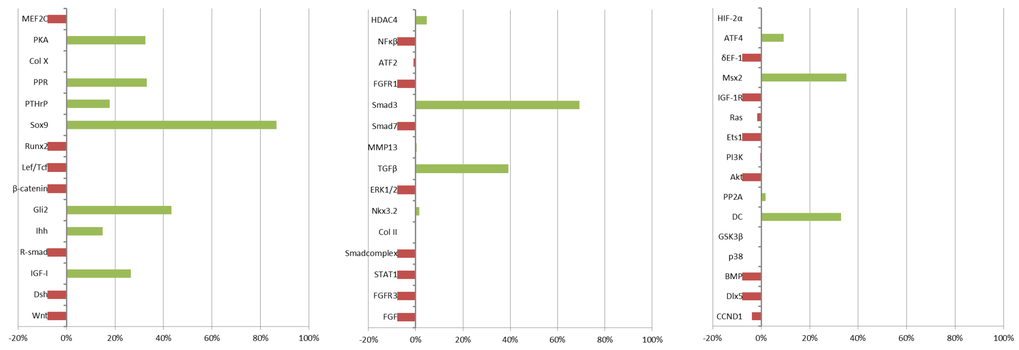

Figure 3: Green bars indicate a positive effect on stability, red bars indicate a detrimental effect

DISCUSSION

- Analysis based on topological information reveals the dominating players in the subsequent stages of endochondral ossification
- Approach can be used to monitor and instruct the formation of cellular constructs containing chondrocytes

HYPERTROPHIC SWITCH

- Upregulation of Smad-1-5-8 is the most efficient way of achieving hypertrophy

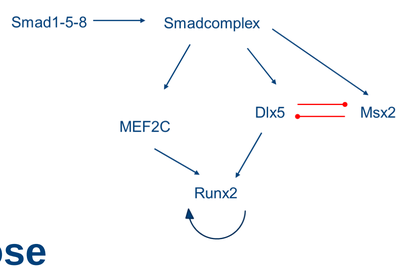

Figure 4: Main mechanism of hypertrophic switch

- Outcome is **dependent on dose**

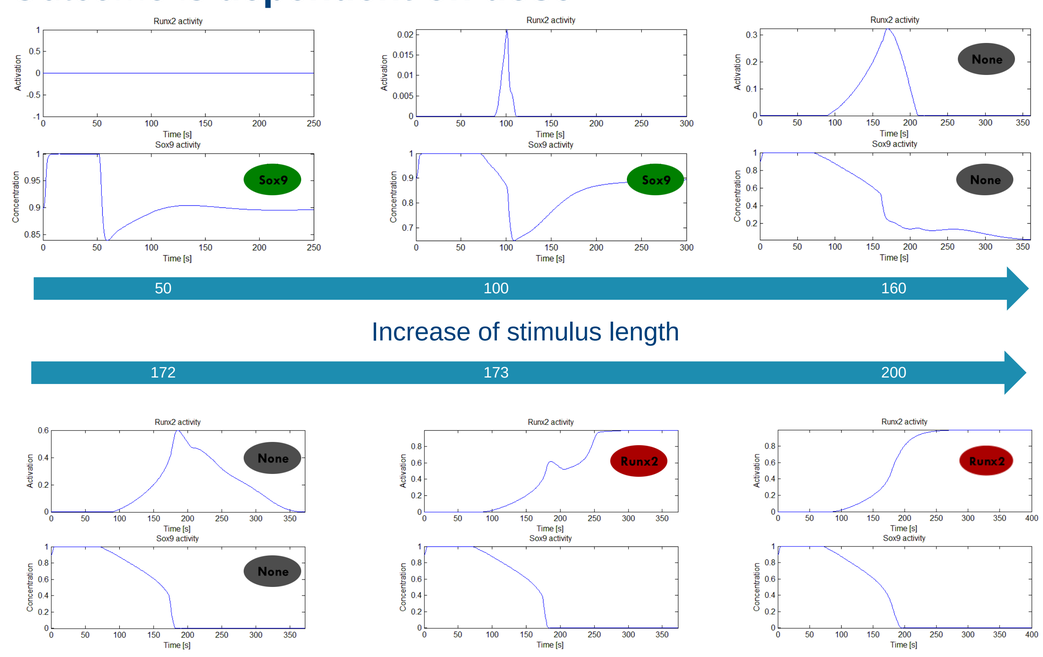

Figure 5: The influence of Smad1-5-8 activation on cell fate depends on the stimulus size

CONTACT DETAILS & REFERENCES

[1] Lenas P. et al. (2009) *Tissue Eng Part B Rev*, **15**, 381.

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